We claim:

1. An isolated estrogen receptor alpha nucleic acid sequence comprising an A908G mutation.

2. An isolated estrogen receptor alpha amino acid sequence comprising a K303R substitution.

3. A method of detecting susceptibility to development of breast cancer in an individual, comprising the steps of:

obtaining a sample from a breast of said individual, wherein said sample comprises a cell having an estrogen receptor alpha nucleic acid sequence; and

assaying said nucleic acid sequence for an A908G mutation, wherein the presence of said mutation in said nucleic acid sequence indicates said individual has breast cancer.

4. The method of claim 3, wherein said sample is from a premalignant lesion of said breast.

5. A method of detecting susceptibility to development of invasive breast cancer in an individual, comprising the steps of:

obtaining a sample from a breast of said individual; and

assaying an estrogen receptor alpha nucleic acid sequence from a cell of said sample for an A908G mutation, wherein the presence of said mutation in said nucleic acid sequence detects susceptibility of said premalignant lesion to develop into said invasive breast cancer.

6. The method of claim 5, wherein said sample is from a premalignant lesion of said breast.

7. A method of detecting susceptibility to development of invasive breast cancer from a premalignant lesion in a breast, comprising the steps of:

obtaining a sample from said premalignant lesion;

dissecting said sample to differentiate hyperplastic cells in said sample from nonhyperplastic cells; and

assaying an estrogen receptor alpha nucleic acid sequence from said hyperplastic cell of said sample for an A908G mutation, wherein the presence

of said mutation in said nucleic acid sequence detects susceptibility of said premalignant lesion to develop into said invasive breast cancer.

8. The method of claim 7, wherein said dissection step comprises removal of said hyperplastic cells from said sample by manual manipulation or by laser capture microdissection.

9. The method of claim 7, wherein said sample is obtained by biopsy.

10. The method of claim 3, wherein said assaying step comprises sequencing, single stranded conformation polymorphism, mismatch oligonucleotide mutation detection, or a combination thereof.

11. The method of claim 3, wherein said assaying step is by antibody detection with antibodies to said A908G mutation of said estrogen receptor alpha nucleic acid sequence or is by antibody detection with antibodies to an acetylated estrogen receptor alpha amino acid sequence.

12. A method of classifying breast cancer in an individual, comprising the steps of:

obtaining from said individual a sample from said breast, wherein said sample contains a cancer cell; and

assaying an estrogen receptor alpha nucleic acid sequence from said cell of said sample for an A908G mutation, wherein the presence of said mutation identifies said breast cancer to be invasive breast cancer.

13. The method of claim 12, wherein said sample is obtained by biopsy.

14. The method of claim 12, wherein said assaying step is selected from the group consisting of sequencing, single stranded conformation polymorphism, mismatch oligonucleotide mutation detection, and a combination thereof.

15. The method of claim 12, wherein said assaying step is by antibody detection with antibodies to said A908G mutation of said estrogen receptor alpha nucleic acid sequence or by antibody detection with antibodies to an acetylated estrogen receptor alpha amino acid sequence.

16. A method of diagnosing breast cancer in an individual, comprising the steps of:

obtaining a sample from a breast of said individual, wherein said sample comprises a cell having an estrogen receptor alpha nucleic acid sequence; and

assaying said nucleic acid sequence for an A908G mutation, wherein the presence of said mutation in said nucleic acid sequence indicates said individual has breast cancer.

17. A method of diagnosing breast cancer in an individual, comprising the steps of:

obtaining a sample from a breast of said individual;

dissecting said sample to differentiate a cell suspected of being cancerous from a noncancerous cell; and

assaying said cell suspected of being cancerous for an A908G mutation in an estrogen receptor alpha nucleic acid sequence, wherein the presence of said mutation in said nucleic acid sequence indicates said individual has breast cancer.

18. The method of claim 17, wherein said dissection step comprises removal of said cells suspected of being cancerous from said sample by manual manipulation or by laser capture microdissection.

19. The method of claim 17, wherein said sample is obtained by biopsy.

20. The method of claim 17, wherein said assaying step is selected from the group consisting of sequencing, single stranded conformation polymorphism, mismatch oligonucleotide mutation detection, and a combination thereof.

21. The method of claim 17, wherein said assaying step is by antibody detection with antibodies to said A908G mutation of said estrogen receptor alpha nucleic acid sequence or is by antibody detection with antibodies to an acetylated estrogen receptor alpha amino acid sequence.

22. A kit for diagnosing an A908G mutation in an estrogen receptor alpha nucleic acid sequence, comprising at least one primer selected from the group consisting of SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:33, SEQ ID NO:34, and SEQ ID NO:35.

23. A monoclonal antibody that binds immunologically to an acetylated estrogen receptor alpha amino acid sequence, or an antigenic fragment thereof.

24. A monoclonal antibody that binds immunologically to an A908G mutation in an estrogen receptor alpha nucleic acid sequence.

25. A method to correct a G mutation at nucleotide 908 of an estrogen receptor alpha nucleic acid sequence in a cell of an individual, comprising the step of administering to said cell an estrogen receptor alpha nucleic acid sequence comprising an A at nucleotide 908.

26. The method of claim 25, wherein said estrogen receptor alpha nucleic acid sequence comprising an A at nucleotide 908 is present on a vector.

27. The method of claim 26, wherein said vector is selected from the group consisting of plasmid, viral vector, liposome, and a combination thereof.

28. The method of claim 27, wherein said viral vector is selected from the group consisting of adenoviral vector, retroviral vector, adeno-associated viral vector, or a combination thereof.

29. A method to prevent breast cancer in an individual, comprising the steps of:

obtaining a sample from a breast of said individual;

identifying in said sample an A908G mutation in a nucleic acid sequence of estrogen receptor alpha; and

correcting said A908G mutation, wherein said correction results in the prevention of said breast cancer.

30. The method of claim 29, wherein said breast sample is from a premalignant lesion of said breast.

31. The method of claim 29, wherein said correction step comprises administering an estrogen receptor alpha nucleic acid sequence comprising a G at nucleotide 908 to a cell comprising an estrogen receptor alpha nucleic acid sequence containing said A908G mutation.

32. A method to treat breast cancer in an individual, wherein an estrogen receptor alpha nucleic acid sequence in a breast cell of said individual has an A908G mutation, comprising the step of administering to said cell an estrogen receptor alpha nucleic acid sequence comprising a G at nucleotide 908.

33. A method to prevent breast cancer in an individual, comprising the steps of:

obtaining a sample from a breast of said individual;

identifying in said sample an arginine at amino acid residue 303 in an amino acid sequence of estrogen receptor alpha; and

administering to said individual an amino acid sequence of estrogen receptor alpha comprising a lysine at amino acid residue 303, wherein said administration results in the prevention of said breast cancer.

34. The method of claim 33, wherein said breast sample is from a premalignant lesion of said breast.

35. A method of identifying a modulator of an estrogen receptor alpha K303R polypeptide, comprising:

(a) providing a candidate modulator;

(b) admixing the candidate modulator with an isolated compound or cell, or a suitable experimental animal;

(c) measuring one or more characteristics of the compound, cell or animal in step (b); and

(d) comparing the characteristic measured in step (c) with the characteristic of the compound, cell or animal in the absence of said candidate modulator,

wherein a difference between the measured characteristics indicates that said candidate modulator is said modulator of the compound, cell or animal.

36. A method of screening for a modulator of an estrogen receptor alpha polypeptide comprising a K303R substitution, comprising:

introducing to a cell:

a vector comprising a nucleic acid sequence which encodes said estrogen receptor alpha K303R polypeptide;

a vector comprising at least one estrogen-responsive regulatory element operatively linked to a reporter polynucleotide; and

a test agent; and

assaying expression of said reporter polynucleotide in the presence of said test agent, wherein said test agent is said modulator when the reporter polynucleotide expression changes in the presence of said test agent.

37. The method of claim 36, wherein at least one of the vectors is transiently transfected into said cell.

38. The method of claim 36, wherein at least one of the vectors is stably transfected into said cell.

39. The method of claim 36, wherein when said expression of the reporter polynucleotide is upregulated, said modulator is an agonist.

40. The method of claim 36, wherein when said expression of the reporter polynucleotide is downregulated, said modulator is an antagonist.

41. The method of claim 36, wherein said cell is a mammalian cell.

42. The method of claim 41, wherein said mammalian cell is selected from the group consisting of CHO, HepG2, HeLa, COS-1, MCF-7, MDA-MB-231, T47D, ZR-75, MDA-MB-435, BT-20, MDA-MB-468, and HEC-1.

43. The method of claim 36, wherein said estrogen-responsive regulatory element is selected from the group consisting of SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42; SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49; SEQ ID NO:22; SEQ ID NO:26, and SEQ ID NO:8.

44. The method of claim 36, wherein said reporter polynucleotide is luciferase, chloramphenicol acetyltransferase, renilla or β-galactosidase.

45. A method of treating breast cancer in an individual comprising the step of administering the antagonist of claim 40 to said individual.

46. A method of identifying a polypeptide which interacts with an estrogen receptor alpha polypeptide comprising a K303R substitution, comprising:

introducing to a cell, a vector comprising a polynucleotide which encodes a chimeric polypeptide comprising said estrogen receptor alpha K303R polypeptide and a DNA binding domain;

introducing to the cell, a vector comprising a polynucleotide which encodes a chimeric polypeptide comprising a candidate polypeptide and a DNA activation domain; and

assaying for an interaction between said DNA binding domain and said DNA activation domain, wherein when said interaction occurs, said candidate polypeptide is said polypeptide which interacts with said estrogen receptor alpha K303R polypeptide.

47. The method of claim 46, wherein said polypeptide which interacts with said estrogen receptor alpha K303R polypeptide is an antagonist of said estrogen receptor alpha K303R polypeptide.

48. The method of claim 46, wherein said interaction is assayed by assaying for a change in expression of a reporter sequence.

49. The method of claim 46, wherein said cell is a yeast cell.

50. The method of claim 46, wherein said cell is a mammalian cell.

51. The method of claim 46, wherein said DNA activation domain and said DNA binding domain are from GAL4 or LexA.

52. The method of claim 46, wherein said reporter sequence is selected from the group consisting of β-galactosidase, luciferase, chloramphenicol acetyltransferase, and renilla.

53. A method of treating an individual for breast cancer, comprising administering the antagonist of claim 47.

54. A method of identifying a peptide which interacts with an estrogen receptor alpha K303R polypeptide, comprising:

obtaining an estrogen receptor alpha K303R polypeptide having an affinity tag and a label;

introducing said polypeptide to a substrate comprising a plurality of bacteriophage, wherein at least one bacteriophage produces at least one candidate peptide; and

determining binding of said polypeptide with said candidate peptide, wherein when said polypeptide binds said candidate peptide, said candidate peptide is said interacting peptide.

55. The method of claim 54, wherein said label is a color label, a fluorescence label, or a radioactive label.

56. The method of claim 54, wherein said affinity tag is biotin, GST, histidine, myc, or calmodulin-binding protein.

57. A method of identifying a compound for the treatment of breast cancer associated with an estrogen receptor alpha K303R polypeptide, comprising the steps of:

obtaining a compound suspected of having said activity; and

determining whether said compound has said activity.

58. The method of claim 57, wherein said compound having said activity is an antagonist of said estrogen receptor alpha K303R polypeptide.

59. The method of claim 58, wherein the method further comprises:

dispersing the compound in a pharmaceutical carrier; and

administering a therapeutically effective amount of the compound in the carrier to an individual having said breast cancer.

60. As a composition of matter, the compound obtained by the method of claim 57.

61. A pharmacologically acceptable composition comprising:

the compound obtained by the method of claim 57; and

a pharmaceutical carrier.

62. A transgenic mouse comprising an estrogen receptor alpha polynucleotide having an A908G mutation.

63. A transgenic mouse comprising an estrogen receptor alpha K303R polypeptide.